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REMARKS

Claims 1-9, 11-16, 18-23, 26-29, and 32-35 are pending in the present application. Claim 1 has been amended, leaving claims 1-9, 11-16, 18-23, 26-29, and 32-35 for consideration upon entry of the present amendment.

Support for the amendment to claim 1 can be found in claim 1 as originally filed.

No new matter has been added by this amendment. Reconsideration of the claims is requested in view of this amendment and the following remarks.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-9, 11-16, 18-23, 26-29, and 32-35 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over JP 57-167938, GB 1476016, or JP 352102434 taken with JP 11-236334 or JP 52-145509. Applicants respectfully traverse this rejection.

GB 1476016 and JP 52-102434 to Fujita et al. ("Fujita") belong to the same patent family and disclose pharmaceutical compositions comprising oridonin and/or lasiokaurin as antitumor agents. The pharmaceutical compositions are prepared from isolated oridonin and/or lasiokaurin and further comprise a solid or liquid carrier. The anti-tumor activity of the compounds was tested by injecting the compounds into mice containing Erlich ascites tumor cells injected into the peritoneum. Erlich ascites tumor cells are a type of epithelial cell. It is stated that oridonin increased the survival rate of mice having the Erlich ascites tumor cells compared to controls with no injected oridonin. Because lasiokaurin and oridonin have similar chemical structures, it is likely that they have similar biological activity.

JP 57-167938 discloses two new diterpenoids allegedly having carcinostatic activity. The abstract states that oridonin is known to exhibit carcinostatic activity. Carcinostatic activity refers to the ability of oridonin to stop the growth of cancer. There is, however, no teaching as to the types of cancer which may be treated successfully with oridonin. As with the foregoing references, the two new diterpenoids disclosed in this

reference are closely related chemicals which may be expected to have similar biological activity.

JP 11-236334 discloses the use of twenty-three plants or their extracts as cell adhesion inhibitors or cancer metastasis inhibitors; the plants include, inter alia, Humulus lupulus. Cancer metastasis inhibitors are compounds that can prevent the spread of cancer from one part of the body to the other. There is, however, no disclosure as to the types of cancer for which the plant extracts act as inhibitors. Furthermore, this patent describe 23 plant extracts as adhesion/metastasis inhibitors and as anti cancer remedies. This reference does not describe the chemical contents of the extracts In addition, the anti adhesion and anti metastasis activity relates only to secondary tumor formation. This reference does not demonstrate the inhibition of the growth of primary tumors.

JP 52-145509 alleges that "a bitter principle of hops of Humulus lupulus," prepared by aqueous extraction of dried hops, exhibits an anti-cancer effect for cancers of the stomach, liver, lung, and breast. This patent discloses only an aqueous extract of Humulus lupulus as the anti cancer preparation. However, there are active components in hops which cannot be extracted by water and can only be extracted by alcohol or organic solvents. Furthermore, there is no teaching as to how to isolate specific chemicals from the extract.

Claim 1 is directed to a composition for treating or preventing prostate cancer or breast cancer, comprising oridonin, a pharmaceutically acceptable salt or ester of oridonin, or a selectively substituted analog of oridonin, and lupulone, a pharmaceutically acceptable salt or ester of lupulone, a selectively substituted analog of lupulone, or a combination thereof. While the cited references appear to suggest the use of oridonin and its closely chemically related analogs , or an extract of Humulus lupulus to treat cancer, these references do not provide the motivation to combine oridonin and lupulone as the Applicants have done. The chemical structure and biological activity of oridonin and lupulone are very different from each other. They are not analogs. The rationale for the Applicant to choose this combination is described below:

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First, the antiproliferative activities of oridonin and lupulone were demonstrated in Figures 1 to 3 (cell growth-inhibition) for a prostate cancer cell line, LNCaP, which expresses androgen receptors (AR positive), for a prostate cancer cell line, DU-145, which does not express androgen receptors (AR negative), and for a breast cancer cell line, MCF-7, which also expresses androgen receptors. All three cancer cell lines contain estrogen receptor beta (i.e., ER beta). Therefore, oridonin and lupulone are expected to have anticancer activities for prostate and breast cancer cells.

Second, each of oridonin and lupulone induced apoptosis in prostate cancer cell lines (Figure 5 and amendment submitted Feb 6, 2004). Thus, mechanistically, both oridonin and lupulone inhibit cancer cell growth by an apoptotic mechanism.

Third, it is shown in the present application that the anti-cancer activity of lupulone is directed at the inhibition of primary tumor growth. Not only was cancer cell growth inhibited, but the cell cycle of the cancer cells was also modulated at specific points in the cell cycle.

In the absence of data regarding the specificity and mechanism of action of various anti-caner agents, it is not obvious which agents can and should be combined. This is at least in part because different anti-cancer agents have specificity for, and may be used to treat, different forms of cancer. When, as in the present case, the two agents to be combined appear to have specificity for different types of cancer, and have not been shown to be useful to treat the same types of cancer, there is no motivation to combine the two agents. In addition, different anti-cancer agents act by different mechanisms and may have antagonistic or synergistic effects.

An Examiner cannot establish obviousness by locating references that describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would have impelled one skilled in the art to do what the patent applicant has done. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. Int. 1993). The references, when viewed by themselves and not in retrospect, must suggest the invention. *In Re Skoll*, 187 U.S.P.Q. 481 (C.C.P.A. 1975).

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Regarding oridonin, there are three cited references that disclose the use of oridonin. GB 1476016 and JP 52-102434 disclose the use of oridonin to treat Erlich ascites tumor cells, a type of epithelial cell. JP 57-167938 discloses only general carcinostatic activity of oridonin and does not teach the types of cancer for which oridonin has specificity. Regarding lupulone, there are two references that teach the use of Humulus Lupulus extract to treat cancer. JP 11-236334 does not teach the types of cancer for which Humulus lupulus extract is a cancer metastasis inhibitor. JP 52-145509 teaches that Humulus lupulus aqueous extract is effective for cancers of the stomach, liver, lung, and breast. Since lupulone can not simply be extracted from aqueous solution (i.e., it dissolves in alcohol), the JP 52-145509 patent does not appear to describe an extract comprising lupulone. Furthermore, there is no overlap between the cancer-type specificity of oridonin and lupulone. Applicant submits that there is no motivation provided by the references to combine these agents as in the present application.

It is well known in the pharmaceutical arts that different types of cancer respond differently to different anti-cancer agents. (See, for example, EXHIBIT 1 from Cell: A Molecular Approach). The type of treatment used to treat cancer depends, in part, on the type of cancer. (See, for example, EXHIBIT 2, www.bymyside.com/treatment/types_treatment.jsp) Combinations of anti-cancer agents should be chosen, at least in part, based on the type of cancer to be treated. One of ordinary skill in the art, when designing a combination anti-cancer therapy, would consider the cancer-type specificity and mechanism of action of each of the individual anti-cancer agents. Considering that, based on the cited references, oridonin and lupulone have specificity for different types of cancer, one of ordinary skill in the art would not be motivated to combine oridonin and lupulone as the Applicant has done.

The cited references also provide no expectation of success for the combination of oridonin (or salt, ester, or analog thereof) and lupulone (or salt, ester, or analog thereof) recited in Applicants' Claim 1. According to Todd R. Goulb, over the last 25 years "no new drugs have entered standard treatment protocols; rather it has been the optimization of combinations of old drugs, based entirely on clinical empiricism and trial and error". (EXHIBIT 3, Mining the genome for combination therapies) This statement suggests

that optimization of drug combinations is not straightforward and in fact requires "clinical empiricism and trial and error". In fact, certain combinations of anti-cancer agents can have antagonistic effects. For example, antimitotic agents such as paclitaxel and G_1-S arresting agents such as 5-fluorouracil have antagonistic effects. (Johnson et al. Clinical Cancer Research 5, 2559-2565, 1999, EXBIBIT 4) In this case, the G_1-S arresting agent interfered with the ability of the antimitotic agent to induce apoptotic cell death. Thus, without some knowledge of the mechanism of action of the particular anti-cancer agents and/or clinical data, one of ordinary skill in the art would not simply combine any two anti-cancer agents.

The present application, in contrast to the cited references, provides ample support for the use of a combination of oridonin and lupulone to treat breast and prostate cancer. As shown in the Examples of the present application, oridonin affects the cell cycle of LNCAP androgen receptor positive prostate cancer cells at the G1 phase; it affects the cell cycle of DU-145 androgen receptor negative cells at the G2M phase; and it affects the cell cycle of MCF-7 breast cancer cells at the S phase. Lupulone affects the cell cycle of LNCAP androgen receptor positive prostate cancer cells at the G2M phase and induces a strong apoptosis; and it affects the cell cycle of MCF-7 breast cancer cells at the G1 phase. It was further shown in the present application that oridonin down-regulates Bcl-2 and up-regulates Bax and p53, which ultimately leads to an apoptotic cascade in the cancer cells. As such, both oridonin and lupulone complement each other in inducing apoptosis of the targeted cancer cells at various cell cycle stages.

It has thus been shown by the Applicants that oridonin and lupulone affect prostate and breast cancer cells by affecting the cell cycle in a similar manner. Based on the Applicants' data, it is not expected that oridonin and lupulone will have antagonistic effects, and in fact, they may have synergistic effects. Thus, Applicants have demonstrated that oridonin and lupulone may be combined to treat prostate and breast cancer.

In making the rejection, the Examiner states "Applicant has argued that the components of the claimed composition are not taught in the references as being extracts

but it is clear from the references themselves that they are from plants making them plant extracts by definition". (February 9, 2004 Office Action, Page 2) Applicant believes the Examiner is referring to the statement in the November 2003 Amendment with RCE that "JP 57167938, GP1476016, and JP 352102434, describe the use of isolated compounds and therefore teach away from the use of oridonin-containing extracts". Applicants concede that JP 57167938, GP1476016, and JP 3521024 teach compounds isolated from plants, however, Applicants would characterize these isolates as isolated compounds and not as plant extracts because these extracts appear to be substantially pure. Support for this interpretation can be found, for example, in GP1476016 where the use of the isolated effective components (i.e., oridonin and lasaiokaurin) is distinguished from the compounds in "compounded or impure form", i.e., an extract. Similarly, JP 57167938 describes the purification of oridonin from a plant extract. Thus, the references for oridonin do not describe the use of crude plant extracts, but instead describe the use of oridonin which has been isolated from a crude plant extract. These references are distinctly different from the references cited for lupulone in which an extract from Humulus lupulus is described, with no indication given that any components, let alone lupulone, were purified from the extract. Thus, when the references are considered as a whole – as they must be -- the different forms of the respective compositions teach away from the suggested combination of references. One of ordinary skill in the art would not combine a purified compound (i.e., oridonin) with a crude extract (i.e., an extract of Humulus lupulus) as suggested by the Examiner. Thus, there is no motivation to combine the references.

The Examiner further states "Applicant argues that the Examiner has not considered their argument concerning expectation of success but the fact of the matter is that all the references each teach that oridonin and lupulone are known in the art individually to be used as anti-cancer/carcinostatic agents". (February 9, 2004 Office Action, Page 2) As explained in detail above, the mere disclosure that two compounds have some anti-cancer activity does not provide the motivation to combine the compounds, especially when the two compounds belong to different chemical classes with different biological activity. In fact, depending on the mechanism of action of the two anti-cancer compounds, the compounds may well have antagonistic effects. Further,

the disclosure of a compound for the treatment of one type of cancer is not sufficient to suggest that the compound is suitable to treat other types of cancer. Depending upon the type of cancer and the mechanism of action of the particular anti-cancer agents, some agents may be combined, while others would not and should not be combined. The cited references do not teach the use of oridonin and lupulone to treat the same types of cancer nor do they teach the mechanism of action of oridonin and lupulone. Further, the references do not provide any motivation to combine oridonin and lupulone. Thus, the Examiner's statement regarding expectation of success is not understood. Applicants maintain that the references themselves do not provide an expectation of success for the combination of oridonin and lupulone.

Regarding JP 11-236334, the Examiner states that Applicant argues that "Humulus lupulus is only one of a number of extracts listed but the reference very clearly states that Humulus lupulus is used and can be used". (February 9, 2004 Office Action, Page 2) Applicants maintain that JP 11-236334 discloses a large number of plant extracts having utility as cancer metastasis inhibitors, but not antiprolferative or apoptosis inducing agents. There is no motivation in JP 11-236334 to combine any of the disclosed plant extracts with other anti-cancer agents. Further, there is no motivation to select Humulus lupulus over any other of the plant extracts listed in the reference to combine with any other anti-cancer agent, let alone oridonin.

Lastly, the Examiner states regarding the previously cited case law "These cases are routinely used in pharmaceutical arts and this case involves a plant extract which does not need FDA approval, so technically it is a natural pharmaceutical not as applicant has suggested". (February 9, 2004 Office Action, Page 2) Applicants do not understand this comment, particularly the Examiner's reference to the FDA. Applicants are seeking a patent, not FDA approval. Further, Applicants are claiming a composition "wherein the composition is suitable for the treatment or prevention of prostate cancer and breast cancer". Whether a "natural pharmaceutical" or a "non-natural pharmaceutical" Applicants maintain that a composition suitable for the treatment of various cancers is a pharmaceutical composition. Similar to synthetic pharmaceuticals, the development of natural pharmaceuticals also requires an effort to conduct laboratory research and obtain

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proprietary knowledge. It is well-established that the pharmaceutical arts are highly unpredictable. The references cited by the Examiner are not particularly relevant to the unpredictable pharmaceutical arts. *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (C.C.P.A. 1972)(relating to a combination of surfactants); *In re Susi*, 58 CCPA 1074, 1079-80, 169 USPQ 423, 426 (C.C.P.A. 1971)(relating to light stable polymers); *In re Crockett*, 279 F.2d 274, 276-277, 126 USPQ 186, 188 (C.C.P.A. 1960)(relating to use of magnesium oxide and calcium carbide in cast iron). Thus, Applicants maintain that the pharmaceutical arts, and in particular anti-cancer treatments, are very unpredictable.

For at least these reasons, Applicants maintain that a prima facie case of obviousness has not been established. Applicants respectfully request the reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a).

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance is requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130 maintained by Cantor Colburn LLP.

Respectfully submitted,

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